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Drug survival of adalimumab, ustekinumab and secukinumab in patients with psoriasis: a prospective cohort study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR)

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Summary

Background Real-world biologic drug survival is an important proxy measure for effectiveness. Predictors of drug survival may help patients with psoriasis choose between biologic therapies.

Objectives (i) To assess the relative drug survival of adalimumab, ustekinumab and secukinumab in patients with psoriasis. (ii) To investigate predictors of biologic drug survival.

Methods A prospective cohort study was performed in the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) between November 2007 and August 2019. We performed survival analysis and fitted a flexible parametric survival model for biologic discontinuation due to ineffectiveness.

Results In total 9652 patients were included: 5543 starting on adalimumab (57·4%), 991 on secukinumab (10·3%) and 3118 on ustekinumab (32·3%). The overall drug survivals of adalimumab, secukinumab and ustekinumab in year 1 were 0·78 [95% confidence interval (CI) 0·77–0·79], 0·88 (95% CI 0·86–0·91) and 0·88 (95% CI 0·87–0·89), respectively. The adjusted hazard ratios (adjHRs) for discontinuation of adalimumab and secukinumab compared with ustekinumab were 2·11 (95% CI 1·76–2·54) and 0·67 (95% CI 0·40–1·11), respectively. The presence of psoriatic arthritis predicted for survival in the adalimumab and secukinumab cohorts (adjHR 0·67, 95% CI 0·51–0·88 and 0·70, 95% CI 0·40–1·24, respectively), but for discontinuation in the ustekinumab cohort (adjHR 1·42, 95% CI 1·12–1·81). Previous exposure to biologic therapies predicted for discontinuation in the ustekinumab and secukinumab cohorts (adjHR 1·54, 95% CI 1·26–1·89 and 1·49, 95% CI 0·91–2·45, respectively) and for survival in the adalimumab cohort (adjHR 0·71, 95% CI 0·55–0·92).

Conclusions Secukinumab and ustekinumab have similar sustained drug survival, while adalimumab has a lower drug survival in patients with psoriasis. Psoriatic arthritis and previous biologic experience were predictors with differential effects between the biologic therapies.

What is already known about this topic?

- There is conflicting evidence over the real-world drug survival of secukinumab in patients with psoriasis.
- Data from registries to date suggest that secukinumab has a lower drug survival than that reported from clinical trials.

What does this study add?

- This study found that secukinumab and ustekinumab had similar sustained drug survival in the real world, while the drug survival of adalimumab was lower, suggesting that the real-world drug survival of secukinumab is higher than previously reported.
- We found that psoriatic arthritis and previous biologic experience had differential effects on drug discontinuation in the three biologic cohorts. These predictors may help patients and clinicians choose the most appropriate biologic therapy.

Biologic therapies are the current standard of care for patients with moderate-to-severe psoriasis. Patients treated with biologic therapies in the real world often have to discontinue treatment and/or switch biologic agents over time due to loss of effectiveness or the development of adverse events. Our group has shown that there is only a 53%[1] to 58%[2] probability that patients with psoriasis will remain on a biologic therapy for at least 3 years. Treatment failure leads to disease flares and reduced quality of life, as well as higher costs to the healthcare system.[3]

Drug survival, or persistence, is a proxy measure for the effectiveness, safety and tolerability of a medicine. This is defined by the duration of time from initiation to discontinuation of therapy. A recent systematic review and meta-analysis identified different predictors of biologic drug survival in psoriasis across 16 cohort studies, including female sex and obesity, which predicted for discontinuation, and psoriatic arthritis (PsA), which predicted for persistence.[4] Identifying predictors of differential biologic survival may have the potential to help patients and clinicians identify the right biologic first time, and therefore avoid or delay treatment failure.

Our objectives were firstly, to report on the drug survival of the three most commonly used biologic therapies for psoriasis in the UK and the Republic of Ireland – adalimumab, secukinumab and ustekinumab; and secondly, to identify clinical predictors that affect their drug survival. To achieve our objectives we used data from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR), a large, representative, national, prospective psoriasis registry, to perform descriptive and survival analyses for the three biologic therapies, and to develop an adjusted flexible parametric model.

Patients and methods

Data source and study population

The structure and study design of BADBIR and the baseline characteristics of the patients recruited have been reported previously.[5,6] Briefly, BADBIR is a large, ongoing pharmacovigilance registry of patients with psoriasis in the UK and the Republic of Ireland that was established in September 2007. To date, 164 secondary-care dermatology centres have contributed data to BADBIR. The National Institute for Health and Care Excellence recommends that all patients with psoriasis on biologic therapies in England should be registered on BADBIR. Patients are recruited to three different cohorts depending on the drug of initiation: nonbiologic systemic therapies, oral small molecules and biologic therapies. Data are collected 6 monthly for the first 3 years, then annually thereafter. Detailed information is collected at baseline and follow-up. Importantly, details of the biologic therapies, including start and stop dates, reasons for discontinuation and gaps in treatment, are obtained during follow-up visits. Data from the start of the registry until August 2019 were used in this study.

Data analysis

Patients eligible for this study had chronic plaque psoriasis, and were recruited or switched to the biologic cohort starting either adalimumab (Humira), secukinumab (Cosentyx) or ustekinumab (Stelara). Patients contributed data to the study if they had one or more follow-up visits. We excluded patients on biologic therapies other than the three drugs listed above. We also excluded patients who did not initiate the three biologic therapies at registration to ensure better capture of baseline predictors. We used the same definition for drug survival as in our previous studies,[1] with discontinuation of therapy defined as any gap in treatment for more than 90 days. We censored patients at the last available follow-up date. Reasons for discontinuation were classified as ineffectiveness, adverse events or others.

We performed a descriptive summary of the baseline characteristics of the three biologic cohorts, and report the number of missing values in each cohort. We also performed a descriptive summary of all adverse events leading to biologic

discontinuation, which were reported and coded using the Medical Dictionary for Regulatory Activities (MedDRA) classification. Data points with fewer than five participants were censored due to data confidentiality. Biologic drug survival was examined using Kaplan–Meier survival analysis, and survival functions at 1 and 2 years were reported. Biologic drug survival was stratified by the reasons for discontinuation.

Model development

The model for the outcome of biologic discontinuation due to ineffectiveness was utilized as a proxy for biologic treatment failure. We identified a priori potential predictors for drug survival or discontinuation from our previous studies, clinical observations and a systematic review.[4] We used a two-tier predictor selection process. The first tier identified covariates that were consistently found to be associated with biologic drug survival in psoriasis across different studies. These covariates were age, sex, body mass index and PsA. We included other covariates in the second tier, which included predictors in some but not previous studies of drug survival, as well as other covariates that were not previously evaluated. These covariates were the previous biologic exposure status, Psoriasis Area and Severity Index, smoking intake, alcohol intake, chronic obstructive pulmonary disease, type 1 diabetes, number of comorbid conditions, needing to use methotrexate or ciclosporin concomitantly during biologic therapy, waist circumference, nail psoriasis, palmoplantar psoriasis, flexural psoriasis, scalp psoriasis and unstable psoriasis. We investigated obesity ($\geq$ 30 kg m^{-2}), previous biologic exposure status, diabetes, palmoplantar psoriasis, flexural psoriasis, diabetes, sex and PsA, which were the selected dichotomous predictors, for effect modification with biologic therapy on drug discontinuation.

A flexible parametric survival model was fitted using the stpm2 command in Stata (StataCorp, College Station, TX, USA) to adjust for and identify predictors of discontinuation. In contrast to Cox regression models, which are semiparametric and do not estimate the baseline hazard function (equivalent to the hazard function when all covariates are set to zero), this method uses a parametric modelling approach, and restricted cubic splines are fitted to model the baseline hazard. This approach allows for estimation of the absolute measures of risk in time-to-event data, as well as the modelling of nonproportional effects of covariates.[7] The number of knots for the restricted cubic spline function was selected to give the smallest Akaike information criterion and the Bayesian information criterion, which are criteria for model selection based on the likelihood function.

We tested for nonproportionality of the comparative biologic survival by comparing two models, one of which allows for time-dependent effects of the biologic therapies, with the likelihood ratio test. Missing data were accounted for with 20 multiply imputed datasets. We used the mfpmi command in Stata[8] to test the second-tier covariates for inclusion in the model using backward stepwise regression (P-value of 0·1 as the cutoff), along with testing for fractional polynomial transformation for continuous predictors to account for nonlinearity, while all first-tier covariates were forced into the model. Model fit, calibration and discrimination were also evaluated. The model's fit, which measures how much of the variation in the outcome is explained by the model, was assessed by the Royston and Sauerbrei R^2_D. Model calibration, which measures the agreement between the observed outcomes and the predicted outcomes, was assessed by the calibration slope. Model discrimination, which measures how well the model separates individuals who discontinue the biologic therapy from those who do not, was assessed by the Harrell *C*-statistic.

Sensitivity analysis

A sensitivity analysis restricting the time period to when all three biologic therapies were available in BADBIR was performed. All analyses were performed using Stata 15·1. The study was reported according to the STROBE guidelines.

Ethical approval

BADBIR was approved in March 2007 by NHS Research Ethics Committee North West England, reference 07/MRE08/9. All individuals gave written informed consent for their participation in the registry.

Results

In total 9652 patients were eligible for inclusion, with 5543 (57·4%) starting on adalimumab, 991 (10·3%) on secukinumab and 3118 (32·3%) on ustekinumab. The overall median age of the cohort was 45·0 years [interquartile range (IQR) 35·0–54·0], with a median body mass index of 30·0 kg m^{-2} (IQR 26·1–34·9) and a median Psoriasis Area and Severity Index of 15·4 (IQR 10·7–18·9). The baseline characteristics of the cohort separated by biologic therapy, along with the proportions of missing data, are presented in Table 1. Notable differences between the three biologic cohorts included the proportion of patients with PsA (adalimumab 22·7%, secukinumab 22·8%, ustekinumab 15·5%), the proportion of biologic-naive patients (adalimumab 86·3%, secukinumab 72·9%, ustekinumab 74·8%) and the proportion of patients on concomitant methotrexate during follow-up (adalimumab 15·1%, secukinumab 7·2%, ustekinumab 9·4%).

Adalimumab had the longest accrued follow-up time, with a median of 2·0 years (IQR 0·8–4·2), followed by ustekinumab with a median of 1·9 years (IQR 0·8–3·6). Secukinumab had the shortest follow-up time, with a median of 1·0 years (IQR 0·5–1·8). The survival functions for the three biologic cohorts are listed in Table 2. Broadly, secukinumab and ustekinumab had similar sustained survival functions after 1 and 2 years across the different reasons for discontinuation. Comparatively, adalimumab had the lowest survival function at all timepoints and across all reasons for discontinuation (i.e. for both ineffectiveness and adverse events) (Table 2). A

Table 1 Baseline demographic and disease characteristics of the three biologic cohorts

Baseline characteristic	Adalimumab (n = 5543)	Secukinumab (n = 991)	Ustekinumab (n = 3118)
Age (years)	45·0 (35·0–53·0)	47·0 (36·0–55·0)	45·0 (35·0–55·0)
Female sex	2288 (41·3)	385 (38·8)	1257 (40·3)
Body mass index (kg m^{-2})	29·7 (26·1–34·3)	30·4 (26·6–35·1)	30·3 (26·1–35·8)
Missing	336 (6·1)	52 (5·2)	195 (6·3)
Waist circumference (cm)	100·0 (90·0–111·0)	102·0 (92·0–114·0)	102·0 (91·0–114·0)
Missing	579 (10·5)	139 (14·2)	388 (12·5)
Alcohol units per week	3·0 (0·0–12·0)	3·0 (0·0–10·0)	3·0 (0·0–10·0)
Alcohol intake by category			
No documented alcohol intake	1704 (30·7)	366 (36·9)	1085 (34·8)
Lower-risk drinking[a]	2717 (49·0)	484 (48·8)	1523 (48·8)
Hazardous drinking[b]	576 (10·4)	101 (10·2)	302 (9·7)
Harmful drinking[c]	85 (1·5)	10 (1·0)	54 (1·7)
Missing	461 (8·3)	30 (3·0)	154 (4·9)
Smoking status			
Never smoked	1836 (33·1)	361 (36·4)	1076 (34·5)
Previous smoker	1838 (33·2)	360 (36·3)	1114 (35·7)
Current smoker	1436 (25·9)	251 (25·3)	802 (25·7)
Missing	433 (7·8)	19 (1·9)	126 (4·0)
Number of cigarettes smoked per day	0·0 (0·0–4·0)	0·0 (0·0–2·0)	0·0 (0·0–3·0)
Disease duration (years)	20·0 (12·0–29·0)	19·0 (10·0–30·0)	20·0 (11·0–30·0)
Baseline DLQI	18·0 (12·0–24·0)	18·0 (12·0–23·0)	18·0 (12·0–23·0)
Missing	2479 (44·7)	370 (37·3)	1398 (44·8)
Baseline PASI	14·0 (10·8–19·1)	13·6 (10·6–18·9)	13·6 (10·5–18·6)
Missing	683 (12·3)	111 (11·2)	330 (10·6)
Psoriatic arthritis	1257 (22·7)	226 (22·8)	483 (15·5)
Nail psoriasis	3090 (55·7)	504 (50·9)	1604 (51·4)
Palmar psoriasis	1034 (18·7)	183 (18·5)	578 (18·5)
Scalp psoriasis	3902 (70·4)	693 (69·9)	2237 (71·7)
Flexural psoriasis	2076 (37·5)	331 (33·4)	1131 (36·3)
Unstable psoriasis	607 (11·0)	101 (10·2)	317 (10·2)
Number of previous biologic therapies			
0	4781 (86·3)	722 (72·9)	2333 (74·8)
1	606 (10·9)	162 (16·3)	476 (15·3)
2	125 (2·3)	72 (7·3)	217 (7·0)
≥ 3	31 (0·6)	35 (3·5)	92 (3·0)
Any treatment with methotrexate during follow-up	839 (15·1)	71 (7·2)	294 (9·4)
Any treatment with ciclosporin during follow-up	315 (5·7)	16 (1·6)	142 (4·6)
Number of comorbid conditions			
0	1510 (27·2)	311 (31·4)	867 (27·8)
1–2	2953 (53·3)	499 (50·4)	1552 (49·8)
3–4	898 (16·2)	144 (14·5)	544 (17·4)
≥ 5	182 (3·3)	37 (3·7)	155 (5·0)
COPD	94 (1·7)	24 (2·4)	79 (2·5)
Diabetes	468 (8·4)	119 (12·0)	352 (11·3)
Dyslipidaemia	530 (9·6)	74 (7·5)	296 (9·5)
Hypertension	1304 (23·5)	232 (23·4)	797 (25·6)

The data are presented as the median (interquartile range) or n (%). COPD, chronic obstructive pulmonary disease; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index. [a]Lower risk: < 21 units per week in men, < 14 units per week in women. [b]Hazardous: 21–49 units per week in men, 14–34 units per week in women. [c]Harmful: ≥ 50 units per week in men, ≥ 35 units per week in women.

Kaplan–Meier plot summarizing drug survival due to either ineffectiveness or adverse events for all three biologic therapies is presented in Figure 1.

The adverse events that led to biologic discontinuation are presented Table S1 (see Supporting Information), coded by the MedDRA system organ classification. The three most common codes for adverse events were infections and infestations, surgical and medical procedures, and general disorders and administration-site conditions. Fewer than five event codes of noninfective colitis were present in the secukinumab and ustekinumab cohorts, while there were eight in the adalimumab cohort. There were fewer than five events coded as fungal infections in the secukinumab cohort, with none in either the adalimumab or ustekinumab cohorts. The reasons for discontinuation other than ineffectiveness or adverse events are summarized in Table S2 (see Supporting Information).

Table 2 Survival functions at years 1 and 2 for the three biologic cohorts stratified by reason for drug discontinuation

	Adalimumab (n = 5543)		Secukinumab (n = 991)		Ustekinumab (n = 3118)	
Reasons for discontinuation	Total participants/ discontinuations	Survival function (95% CI)	Total participants/ discontinuations	Survival function (95% CI)	Total participants/ discontinuations	Survival function (95% CI)
All reasons						
Year 1	3818/1155	0·78 (0·77–0·79)	510/82	0·88 (0·86–0·91)	2169/330	0·88 (0·87–0·89)
Year 2	2793/556	0·66 (0·64–0·67)	199/53	0·77 (0·73–0·80)	1484/233	0·77 (0·76–0·79)
Ineffectiveness						
Year 1	3818/628	0·87 (0·86–0·88)	510/44	0·93 (0·91–0·95)	2169/156	0·94 (0·93–0·95)
Year 2	2793/301	0·80 (0·78–0·81)	199/28	0·87 (0·84–0·90)	1484/107	0·89 (0·87–0·90)
Adverse events						
Year 1	3818/323	0·93 (0·93–0·94)	510/28	0·96 (0·95–0·97)	2169/103	0·96 (0·95–0·97)
Year 2	2793/143	0·89 (0·88–0·90)	199/12	0·93 (0·91–0·95)	1484/60	0·93 (0·92–0·94)
Others						
Year 1	3818/204	0·96 (0·95–0·96)	510/10	0·98 (0·97–0·99)	2169/71	0·97 (0·97–0·98)
Year 2	2793/112	0·92 (0·92–0·93)	199/13	0·94 (0·91–0·96)	1484/66	0·94 (0·93–0·95)

CI, confidence interval.

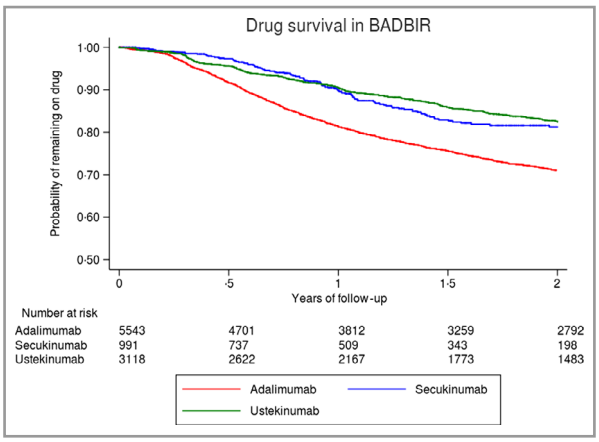

Figure 1. Crude drug survival for discontinuation due to either ineffectiveness or adverse events in the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR).

We stratified crude drug survival in the three biologic cohorts by PsA (Table S3; see Supporting Information) and by previous biologic exposure (Table S4; see Supporting Information). There was higher drug survival in the adalimumab PsA cohort, while for ustekinumab drug survival was higher in the cohort without PsA. Both secukinumab and ustekinumab had lower drug survival in the biologic-experienced cohort compared with the biologic-naive cohort, while for adalimumab there was little difference. The sensitivity analysis restricting the cohort to those participants starting biologics after 1 September 2013 found similar drug survival to the main analysis (Table S5; see Supporting Information).

Model development and performance

Univariable analysis for each covariate is presented in Table S6 (see Supporting Information). Effect modification between choice of biologic and both PsA and biologic exposure status was statistically significant, and interaction terms for these covariates were included in the multivariable analysis. Backwards elimination left the covariates of concomitant methotrexate, concomitant ciclosporin, number of comorbidities, waist circumference, palmoplantar psoriasis, flexural psoriasis and diabetes in the multivariable flexible parametric model (Table 3). The adjusted hazard ratios for discontinuation of adalimumab and secukinumab compared with ustekinumab were 2·11 [95% confidence interval (CI) 1·76–2·54] and 0·67 (95% CI 0·40–1·11), respectively. The overall adjusted survival curve standardized for the covariate pattern is presented in Figure S1 (see Supporting Information), and the adjusted survival curves by biologic therapy standardized for the covariate pattern are presented in Figure S2 (see Supporting Information). These adjusted survival curves show similar differential drug survival for the three biologic therapies compared with the Kaplan–Meier plots in Figure 1, but CIs are added for precision around the estimate of drug survival.

Regarding the overall model performance, the Royston and Sauerbrei R^2_D was 0·12 (95% CI 0·10–0·15). The Harrell's C-index for model discrimination was 0·62 (95% CI 0·61–0·63). The calibration slope measuring model calibration was 1·00 (95% CI 0·89–1·11).

Discussion

In our analysis of a large real-world cohort of patients with severe psoriasis, we showed that secukinumab and ustekinumab had similar sustained drug survival over 2 years, and adalimumab had lower drug survival over this period of time. We found that PsA and previous biologic experience were predictors that had a differential effect on the risk of discontinuation due to ineffectiveness in the three biologic cohorts.

The strengths of this study include the use of one of the largest prospective registries for patients with psoriasis in the world to investigate biologic drug survival. It also represents the largest prospective observational real-world cohort study

Table 3 Final multivariable prognostic model for drug survival (discontinuation due to ineffectiveness)

Covariate	Hazard ratio (95% CI)
Age	1·00 (0·99–1·00)
Female sex	1·28 (1·16–1·42) *
Baseline Psoriasis Area and Severity Index	1·01 (1·01–1·02) *
Body mass index (kg m^{-2}) [a]	0·03 (0·01–0·12) *
Number of comorbid conditions[b, c]	1·00 (1·00–1·00)
Waist circumference (cm)	1·00 (1·00–1·01)
Palmoplantar psoriasis	1·12 (0·99–1·27)
Flexural psoriasis	1·12 (1·01–1·24) *
Diabetes	1·34 (1·15–1·57) *
Concomitant methotrexate	1·21 (1·03–1·42) *
Concomitant ciclosporin	2·53 (1·98–3·22) *
Biologic therapies	
Ustekinumab	Reference
Adalimumab	2·11 (1·76–2·54) *
Secukinumab	0·67 (0·40–1·11)
Psoriatic arthritis (ustekinumab)	1·42 (1·12–1·81) *
Psoriatic arthritis (adalimumab)	0·67 (0·51–0·88) *
Psoriatic arthritis (secukinumab)	0·70 (0·40–1·24)
Biologic experienced (ustekinumab)	1·54 (1·26–1·89) *
Biologic experienced (adalimumab)	0·71 (0·55–0·92) *
Biologic experienced (secukinumab)	1·49 (0·91–2·45)

CI, confidence interval. Comparisons of the model fit statistics suggested three knots and one knot to be placed for the restricted cubic splines to model the baseline hazard and the time-dependent effect of biologic treatment, respectively. *Statistically significant results ($P < 0·05$). [a]Body mass index transformation = (body mass index / 10)$^{-2}$. [b]The number of comorbid conditions is the total number from the following conditions: hypertension, angina, myocardial infarction, stroke, epilepsy, asthma, chronic obstructive pulmonary disease, peptic ulcer, renal disease, liver disease, tuberculosis, demyelination, diabetes, impaired glucose tolerance, depression, dyslipidaemia, cancer (excluding skin cancer), immunodeficiency syndromes, thyroid disease and other diseases (any other disease counted as 1). [c]Number of comorbid conditions transformation = [(no. comorbid conditions + 1) / 10]$^{-2}$.

assessing secukinumab in patients with psoriasis to date. Detailed data capture allowed us to differentiate by drug discontinuation reason, which is vital for clinical interpretation of drug survival,[9] as well as allowing for the inclusion of many covariates that are clinically relevant for drug discontinuation.

However, the overall predictive performance of the model was limited. Similarly to our previous work to develop a model using clinical baseline factors to predict serious infection in patients starting biologic therapies,[10] clinical factors appear to be poorly predictive of drug discontinuation due to ineffectiveness. Work by the Psoriasis Stratification to Optimise Relevant Therapy (PSORT) consortium in the UK has identified that pharmacokinetic factors such as early drug levels are important for prediction of later treatment response for adalimumab[11] and ustekinumab,[12] and it may be that the determinants of biologic pharmacokinetics such as propensity to develop antidrug antibodies or other factors affecting distribution and bioavailability of biologic therapies are more predictive of drug ineffectiveness than are clinical covariates. In addition, there may be other unmeasured factors that might be predictive of biologic ineffectiveness, such as genomic and transcriptomic data, and drug adherence. Despite the fact that the secukinumab cohort was smaller and had a shorter follow-up than the adalimumab and ustekinumab cohorts, we report the largest real-world secukinumab cohort to date. Similarly to our previous studies, the Dermatology Life Quality Index[13] could not be included as a covariate due to high levels of missing data.

We found that the effects of having PsA and having previously been treated with biologic therapies varied between the different biologic cohorts. Participants with PsA had a 42% increase in the risk of discontinuing ustekinumab, while there was a similar protective effect against discontinuation for secukinumab and adalimumab. Given that ustekinumab has a lower efficacy for PsA than adalimumab or secukinumab, this result suggests that patients persisted on adalimumab due to additional beneficial effects on PsA. Studies investigating the drug survival and effectiveness of these biologics on a larger cohort of patients with PsA in order to replicate these findings are required. It is important to note that adalimumab had a lower drug survival in patients both with and without PsA compared with the two other biologic therapies (Table S3; see Supporting Information).

Similarly, prior exposure to biologic therapies had a protective effect on drug survival in participants on adalimumab, compared with a negative effect on drug survival in participants on ustekinumab or secukinumab (Table 3). This statistical interaction may be a function of the higher proportion of patients having received three or more biologic therapies in the ustekinumab and secukinumab cohorts compared with the adalimumab cohort (Table 1), and warrants further stratified analysis in each separate line of biologic therapy as more data accrue over time. Further data accrual would also allow for investigation of whether failure due to blockade of a specific pathway might be predictive of loss of effectiveness in these three biologic therapies.

In addition to female sex, concomitant methotrexate and concomitant ciclosporin, which are previously identified predictors for drug discontinuation,[1] diabetes, flexural psoriasis and palmoplantar psoriasis were included as predictors for drug discontinuation (Table 3). Diabetes could reflect an inflammatory burden[14] that is additional to the burden from psoriasis. Flexural and palmoplantar areas of involvement with psoriasis are hard to treat, can be highly symptomatic, and are associated with a higher psychosocial burden given that these areas are either highly visible or have a high impact on quality of life.[15–17] However, these predictors did not have differential effects in the three biologic cohorts.

The Danish DERMBIO registry has reported previously on the drug survival of secukinumab.[18] In the first analysis, published in 2018, the authors found a low drug survival for

secukinumab in 196 treatment series. Treatment series include patients in the analysis multiple times for different drug exposures. Survival functions at specific timepoints were not reported, with the secukinumab follow-up being too short to approximate the 1-year survival function. However, secukinumab was found to have a higher probability of discontinuation due to any cause than ustekinumab (hazard ratio 2·43, 95% CI 1·82–3·25). Only 21·5% of these treatment series were in biologic-naive patients. The same group subsequently published a more recent analysis of their cohort, with 368 patients on secukinumab (40·7% biologic-naive) included in the analysis.[19] The survival functions for secukinumab were not reported in numerical format but approximated to around 85·0% for the biologic-naive cohort and 67·0% for the biologic-experienced cohort at 1 year.

The Dutch BioCAPTURE registry has also reported on the drug survival of secukinumab.[20] The authors found a 1-year drug survival of 76·0% in 196 patients on secukinumab, and, similarly to the DERMBIO registry, only 16·8% of patients on secukinumab were biologic naive, with a median number of biologics before secukinumab of two. In the stratified analysis, biologic-naive patients (n = 33) had a 1-year survival function of 90·0%, while biologic-experienced patients (n = 163) had a 1-year survival function of 74·0%.

The above studies are limited due to small sample sizes and a skew towards selected biologic-experienced patients. Compared with these two registries, in BADBIR patients are treated earlier with secukinumab in their treatment pathway, with a much higher proportion of biologic-naive patients (72·9%) and a significantly larger (n = 991) secukinumab cohort. This explains the more definitive finding of a higher overall drug survival of secukinumab in BADBIR compared with these two registries, although the stratified drug survival between biologic-naive and biologic-experienced patients on secukinumab between BADBIR and BioCAPTURE and DERMBIO are similar.

Contrary to the studies referred to above, the overall persistence in users of secukinumab is similar to that with ustekinumab, which was previously shown to have the highest drug survival compared with adalimumab, infliximab and etanercept in patients with psoriasis. The results in the current study therefore give real-world evidence to support the position of secukinumab as a first-line biologic therapy along with ustekinumab and adalimumab in the British Association of Dermatologists guidelines for biologic therapy for psoriasis published in 2017.[21]

In contrast to the results from the CLEAR randomized controlled trial,[22] which found that secukinumab had higher efficacy for the treatment of psoriasis than ustekinumab, secukinumab did not have a corresponding superior drug survival when compared with ustekinumab in this study. The more frequent monthly dosing regimen of secukinumab compared with the 3-monthly regimen of ustekinumab may explain this discrepancy, as drug survival is a proxy measure not only for drug effectiveness but also for ease of use.

We have identified PsA and previous biologic experience as factors that differentiate between the three biologic therapies. Figure 2(a) shows an example of a typical patient with psoriasis, in whom PsA is a factor that differentiates between the three different biologic therapies, and with the expected drug survival over time adjusted for all other factors. Figure 2(b) shows a similar figure but with the differentiating factor being prior experience of a biologic therapy. Individualized drug survival predictions such as these may help patients and clinicians choose between the three biologic therapies based on these two clinical baseline characteristics.

In conclusion, secukinumab and ustekinumab have similar sustained drug survival that is higher than adalimumab in BADBIR. We identified PsA and previous biologic exposure as factors that have a differential effect on drug survival dependent on the choice of biologic therapy. This information will help patients make an informed decision to start a biologic therapy based on drug survival outcome.

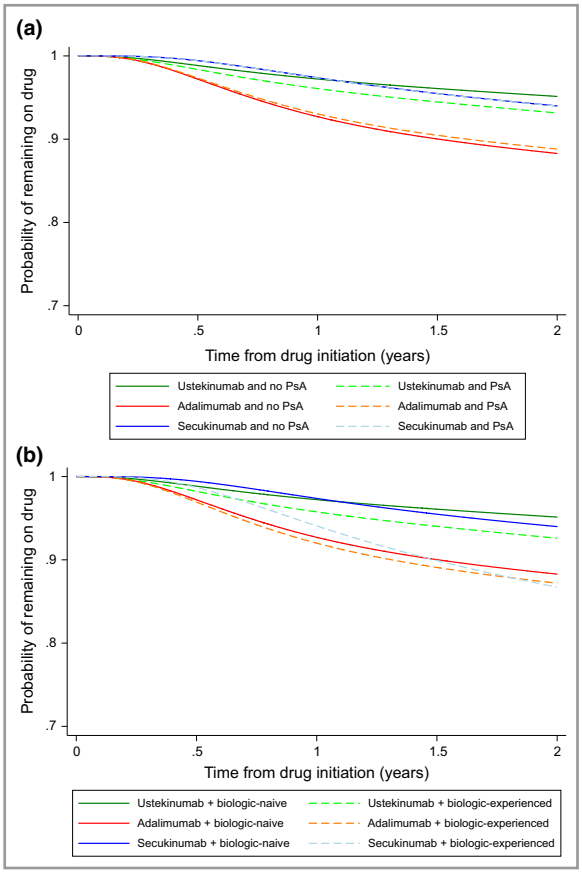

Figure 2. Predicted survival curves from the flexible parametric model for a typical male patient with psoriasis (age 45 years, body mass index 30 kg m^{-2}, waist 101 cm, Psoriasis Area and Severity Index 20, two other comorbid conditions, no flexural or palmoplantar disease, no diabetes, not on concomitant therapies). Survival curves for all three biologic therapies in (a) typical biologic-naive patients with or without psoriatic arthritis (PsA) and (b) typical patients without PsA in either the biologic-naive or biologic-experienced subgroups. The predicted survival curves stratified by treatment with corresponding 95% confidence intervals are presented in Supplementary Figures 3a–c and 4a–c.

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Appendix 1

The BADBIR Study Group includes Jonathan Barker, MD (King's College London); Marilyn Benham (British Association of Dermatologists); Fiona Browne, MB BCh (Crumlin Children's Hospital); A. David Burden, MD (University of Glasgow); Ian Evans, MSc (The University of Manchester); Christopher Griffiths, MD, FMedSci (The University of Manchester); Sagair Hussain, PhD (British Association of Dermatologists); Brian Kirby, MD (St Vincent's University Hospital); C. Elise Kleyn, MD (The University of Manchester); Philip Laws, MBChB (The Leeds Teaching Hospitals NHS Trust); Linda Lawson, MSc (Aberdeen University); Kathleen McElhone, PhD (The University of Manchester); Teena Mackenzie, RN, BSc (Oxford University Hospitals); Tess McPherson, MD (University of Oxford); Kayleigh Mason, PhD (The University of Manchester); Ruth Murphy, PhD (Nottingham University Hospitals); Anthony Ormerod, MD (Aberdeen University); Caroline Owen,

MD (East Lancashire Hospital NHS Trust); Eleanor Pearson (Norfolk & Norwich University Hospitals NHS Foundation Trust); Nick Reynolds, MD (Newcastle University); Josh Richards, PhD (patient representative); Catherine Smith, MD (King's College London) and Richard Warren, PhD (The University of Manchester).

Appendix 2

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Appendix 3

Author contributions. Z.Z.N.Y. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Z.Z.N.Y., M.L., K.J.M., C.E.M.G., R.B.W. Acquisition, analysis and interpretation of data: Z.Z.N.Y., M.L., K.J.M., C.E.M.G., R.B.W., N.J.R., C.H.S., P.J.H. Drafting of the manuscript: Z.Z.N.Y. Critical revision of the manuscript for important intellectual content: Z.Z.N.Y., M.L., K.J.M., C.E.M.G., R.B.W., N.J.R., C.H.S., P.J.H. Statistical analysis: Z.Z.N.Y., M.L. Study supervision: M.L., C.E.M.G., R.B.W.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. Adjusted survival curve standardizing over the covariate pattern of the overall cohort, with the grey shaded area denoting the 95% confidence interval.

Fig S2. Adjusted survival curves standardizing over the covariate patterns for the adalimumab, secukinumab and ustekinumab cohorts, with the dotted lines denoting the 95% confidence intervals.

Fig S3. Predicted survival curves for the patient from Figure 2a-b, a typical male patient with psoriasis (age 45, body mass index 30, waist 101 cm, PASI 20, 2 other comorbid conditions, no flexural/palmoplantar disease, no diabetes, not on concomitant therapies) for all three biologic therapies (biologic-naïve) with or without PsA, stratified by the three therapies with corresponding 95% confidence intervals (dotted lines).

Fig S4. Predicted survival curves for the patient from Figure 2a–b, a typical male patient with psoriasis (age 45, body mass index 30, waist 101 cm, PASI 20, 2 other comorbid conditions, no flexural/palmoplantar disease, no diabetes, not on concomitant therapies) for all three biologic therapies (without PsA) in both biologic-naïve and biologic-experienced subgroups, stratified by the three therapies with corresponding 95% confidence intervals (dotted lines).

Table S1. Adverse events leading to biologic discontinuation, stratified by biologic cohort.

Table S2. All reasons for discontinuation other than ineffectiveness or adverse events.

Table S3. Survival functions of the three biologic cohorts at years 1 and 2 for discontinuation due to ineffectiveness, stratified by psoriatic arthritis status.

Table S4. Survival functions for discontinuation due to ineffectiveness or adverse events for the three biologic cohorts at years 1 and 2, stratified by previous biologic experience.

Table S5. Survival function for discontinuation due to ineffectiveness or adverse events for the three biologic cohorts at years 1 and 2, restricted to all participants starting the drug after 1 September 2013.

Table S6. Univariable (complete-case) analysis of potential predictors of drug survival from flexible parametric survival models with discontinuation due to ineffectiveness as the outcome.